61. (New) The method of Claim 42, further comprising exposing the cell to a chemotherapeutic agent.

62. (New) The method of Claim 42, further comprising exposing the cell to radiation.

REMARKS

Support for new Claims 59-62 is found throughout the specification, e.g., at page 20, line13, page 17, lines 2-4, and page 49, line 30 to page 50, line 5. No question of new matter arises and entry of the new claims is respectfully requested. Claims 28-40 and 42-62 are before the Examiner for consideration.

Rejection under 35 U.S.C. §112, first paragraph

On page 5 of the Office Action, Claims 28-39 and 42-58 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. In particular, the Examiner states that although the specification is enabled for antibody 7C2 blocking and 7C2+FITC binding, it does not provide reasonable enablement for all other antibodies which cross block binding of 7C2 or antibody 7F3 to ErbB2.

Applicants have amended Claims 28, 32, 33, 42, and 58 to recite that the antibody binds to the epitope on ErbB2 to which antibody 7C2 or 7F3 binds. Applicants submit that the claims are sufficiently enabled by the specification at, e.g., page 7, lines 7-9 and Figure 12, which clearly shows that antibodies 7C2 and 7F3 bind to Domain 1. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. §102(b)/103(a)

On pages 3-4 of the Office Action, Claims 38-31, 37-38, 40, 56, and 57 have been rejected under 35 U.S.C. §102(b), or in the alternative, under 35 U.S.C. §103(a) as being obvious over Shepard.

To begin with, Applicants respectfully traverse these rejections on the ground that Shepard teaches away from the presently claimed invention.

The presently claimed invention is directed to methods for inducing cell death by exposing a cell that overexpresses ErbB2 to an isolated antibody that binds to the epitope on ErbB2 to which antibody 7C2 or 7F3 binds (i.e., to Domain 1 of ErbB2) (Claims 28-40 and 42-57 and 59-62) and a method for inducing cell death by exposing a cell that overexpresses ErbB2 to a first antibody that binds to the epitope on ErbB2 to which antibody 7C2 or 7F3 binds (i.e., Domain 1 of ErbB2) and subsequently exposing the cell to a second antibody that does not bind to the binding site of antibody 7C2 or 7F3 (Claim 58).

Shepard teaches the derivation of a family of monoclonal antibodies focused against the extracellular domain of $p185^{HER2}$. (See page 119, left column, lines 16-18). The monoclonal antibodies 4D5, 7C2, and 7F3 are some of these antibodies. (See Table I at page 122). Shepard teaches that these monoclonal antibodies vary in their ability to inhibit proliferation of breast tumor cells, but that 7C2 and 6E9 are consistently less active than the other antibodies in this respect. (See page 120, left column, lines 19-21). Additionally, Shepard discloses that 7C2 has the ability to stimulate the proliferation of several of the tumor cell lines shown in Table III. (See page 120, right column, lines 4-8). Further, when these antibodies were compared for efficacy, as measured by their abilities to inhibit growth of breast and ovarian tumor cells overexpressing $p185^{HER2}$, muAb 4D5 was generally the most

potent and was considered "a good candidate for further characterization." (See page 121, left column, lines 6-9).

Based on these disclosures in Shepard, Applicants submit that one of ordinary skill in the art would not have been motivated to experiment with 7C2 or with antibodies that bind to the same epitope as 7C2 (or 7F3) and surprisingly discover that these antibodies can induce the death of an ErbB2 cell such as by apoptosis as in the present invention. Without motivation, there cannot be a case of obviousness.

First, as set forth above, Shepard teaches that 7C2 is consistently less active in inhibiting the proliferation of breast tumor cells than the other antibodies shown in Table I. One of skill in the art reading this disclosure in Shepard would be motivated to experiment with an antibody other than 7C2 in experiments in which the inhibition or death of cancerous or tumor cells is desired (e.g., a cell which overexpresses ErbB2 as in the present invention). Thus, this disclosure of Shepard teaches away from the present invention. Second, as discussed above, Shepard discloses that 7C2 actually stimulates the proliferation of certain types of cancers. This is the opposite of the presently claimed invention which induces the death of a cell which overexpresses ErbB2 (e.g., a cancer cell). As a result, one of skill in the art would not be motivated to experiment with 7C2, or antibodies that bind to the epitope that 7C2 binds and arrive at the present invention. Thus, Shepard again teaches away from the presently claimed invention. Finally, the disclosure set forth in Shepard that states that muAb 4D5 is the most potent of the $p185^{HER2}$ antibodies set forth in Table I against breast and ovarian tumor cells and is the best candidate for further characterization would certainly motivate one of skill in the art to experiment with 4D5, and not 7C2 or 7F3, or antibodies that bind to the epitope to which 7C2 or 7F3 bind.

In addition, Applicants submit that a disclosure of growth inhibition does not teach or suggest the inducement of cell death as presently claimed. Growth inhibition of cells can occur without cell death occurring. Thus, one of skill in the art would not arrive at the presently claimed invention based on the disclosure of Shepard.

Additionally, Applicants respectfully disagree with the Examiner's assertion in the previous Office Action that the claimed properties of binding to the epitope to which 7C2 or 7F3 bind (i.e., Domain 1 of ErbB2) and 5-50 fold induction of annexin binding are inherent properties of the antibodies 7C2, 7F3, and 4D5 disclosed in Shepard. As discussed above, Shepard teaches the derivation of a family of monoclonal antibodies focused against the extracellular domain of $p185^{HER2}$. (See page 119, left column, lines 16-18). Of these monoclonal antibodies, some were shown to be growth inhibitory, some had no affect on breast or ovarian tumor cell proliferation, and some stimulated the proliferation of breast tumor cells. (See page 120, left column, lines 8-11). Because these monoclonal antibodies were all focused on the extracellular domain of $p185^{HER2}$ and possessed properties that were not always consistent with each other, it cannot be said that all antibodies that bind to the same epitope that 7C2 or 7F3 binds will necessarily have the same properties. Thus, Applicants again submit that Shepard does not teach or suggest methods for inducing cell death by exposing a cell that overexpresses ErbB2 to an isolated antibody that binds to the epitope on ErbB2 to which antibody 7C2 or 7F3 binds as is presently claimed.

Furthermore, Applicants submit that a statement that the properties of antibodies 7C2, 7F3, and 4D5 inherently have the same properties, without more, is insufficient to draw a conclusion that all antibodies that bind to Domain 1, or even to the epitope on Domain 1 where 7C2 and 7F3 bind, will necessarily have the same characteristics (e.g., induce cell

death). For example, classes of antibodies exist in which antibodies have the same binding domain but behave very differently because they have different constant domains. IgG is but one example. Further, although antibodies may be able to bind to the same epitope, binding to that epitope may be conformationally dependent. In other words, binding of a particular antibody to a particular epitope may only occur when a particular region is located next to it, or only if that particular region is folded in a particular manner. The folding of the adjacent region could sterically hinder the binding of antigens to the antibody bound to the epitope, and thus may effect certain characteristics of that antibody (e.g., ability to induce death of a cell).

Additionally, although antibodies 7F3 and 7C2 are mentioned in Shepard (see Figure 2 on page 120), the reference does not enable these particular antibodies. In particular, antibodies 7F3 and 7C2 were not deposited with respect to the reference and their sequences were not disclosed in the reference in such a way that a skilled person could have reproduced those particular antibodies based on the reference. The antibodies 7F3 and 7C2 were not publically distributed or publically available more than one year prior to October 18, 1996, the elective filing date of this application. If an outside investigator had requested samples of the 7F3 or 7C2 antibodies prior to October 17, 1996, Genentech would only have provided the antibodies to the investigator if Genentech was able to approve a research plan proposed by the outside investigator. If the research plan was approved, Genentech would only have provided the research material to the outside investigator under a Material Transfer Agreement (MTA). The standard Genentech MTA at that time imposed restrictions or limitations on the use of the research material. In particular, the laboratory receiving the research material under a Genentech MTA could only use the research material for a research plan approved by Genentech and could not transfer the research material to others outside the laboratory

receiving the research material. The MTA further required that the outside investigator not disclose (orally or in writing) the results of the research until Genentech had been given time to review the disclosure and make recommendations or comment upon it. Thus, 7F3 and 7C2 were not publicly available and the cited reference does not qualify as prior art.

In view of the above, Applicants submit that the present invention is neither anticipated by, nor obvious over, Shepard and respectfully request that these rejections be reconsidered and withdrawn.

Rejection under 35 U.S.C. §102(b)/103(a)

On page 3 of the Office Action, Claims 28-31, 37-38, and 40 have been rejected under 35 U.S.C. §102(b) as being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as being unpatentable over Lewis et al.

Applicants respectfully traverse this rejection in view of the following remarks and submit that Lewis does not teach or suggest the present invention. In particular, Lewis does not disclose methods for inducing cell death by exposing a cell that overexpresses ErbB2 to an isolated antibody that binds to the epitope on ErbB2 to which antibody 7C2 or 7F3 binds (i.e., to Domain 1 of ErbB2) (Claims 28-40 and 42-57) or a method for inducing cell death by exposing a cell that overexpresses ErbB2 to a first antibody that binds to the epitope on ErbB2 to which antibody 7C2 or 7F3 binds (i.e., Domain 1 of ErbB2) and subsequently exposing the cell to a second antibody that does not bind to the binding site of antibody 7C2 or 7F3 (Claim 58).

Although Lewis discloses antibodies 7C2 and 7F3 in passing, Lewis does not teach or suggest the presently claimed invention, i.e., methods for inducing cell death by exposing a

cell that overexpresses ErbB2 to an antibody that binds to the epitope on ErbB2 to which antibody 7C2 or 7F3 binds. As set forth above, a statement that antibodies that bind to the same epitope inherently have the same properties, without more, is insufficient to draw a conclusion that all antibodies that bind to Domain 1, or even to the epitope on Domain 1 where 7C2 and 7F3 bind, will necessarily have the same characteristics (e.g., induce cell death). For example, classes of antibodies exist in which antibodies have the same binding domain but behave very differently because they have different constant domains. IgG is but one example. In addition, although antibodies may be able to bind to the same epitope, binding to that epitope may be conformationally dependent. In other words, binding of a particular antibody to a particular epitope may only occur when a particular region is located next to it, or only if that particular region is folded in a particular manner. The folding of the adjacent region could sterically hinder the binding of antigens to the antibody bound to the epitope, and thus may effect certain characteristics of that antibody (e.g., ability to induce death of a cell).

Further, there is no disclosure present in Lewis to motivate one of skill in the art to experiment with 7C2 or with antibodies that bind to the same epitope as 7C2 (or 7F3) and discover that these antibodies induce the death of an ErbB2 cell as claimed in the present application. Without motivation, there cannot be a case of obviousness.

For example, the results in Lewis suggest that antibody 4D5 is the most potent of the growth-inhibitory antibody and has the most consistent growth-inhibitory activity towards breast tumor cell lines. (See Lewis, p. 256, left column, lines 45-48 and p. 259, right column, lines 1-3). In particular, Lewis notes that 4D5 had superior growth inhibition of SK-BR-3 (i.e., breast cancer cell). However, a disclosure of growth inhibition of cells does not teach or

suggest the inducement of cell death as presently claimed. Thus, one of skill in the art would not arrive at the presently claimed invention based on the disclosure of Lewis. Further, Applicants submit that the disclosures set forth in Lewis would motivate one of skill in the art to experiment with 4D5, and not 7C2 or 7F3, or antibodies that bind to the epitope to which 7C2 or 7F3 bind, and arrive at the present invention (i.e., methods for inducing cell death by exposing a cell that overexpresses ErbB2 to an antibody that binds to the epitope to which 7C2 or 7F3 bind). In fact, these disclosures actually lead one of skill in the art away from the presently claimed invention, i.e., they teach away from the present invention.

Although antibodies 7F3 and 7C2 are mentioned in Lewis, the reference does not enable these particular antibodies. In particular, antibodies 7F3 and 7C2 were not deposited with respect to the reference and their sequences were not disclosed in the reference in such a way that a skilled person could have reproduced those particular antibodies based on the references. The antibodies 7F3 and 7C2 were not publically distributed or publically available more than one year prior to, October 18, 1996, the elective filing date of this application. If an outside investigator had requested samples of the 7F3 or 7C2 antibodies prior to October 17, 1996, Genentech would only have provided the antibodies to the investigator if Genentech was able to approve a research plan proposed by the outside investigator. If the research plan was approved, Genentech would only have provided the research material to the outside investigator under a Material Transfer Agreement (MTA). The standard Genentech MTA at that time imposed restrictions or limitations on the use of the research material. In particular, the laboratory receiving the research material under a Genentech MTA could only use the research material for a research plan approved by Genentech and could not transfer the research material to others outside the laboratory receiving the research material. The MTA

further required that the outside investigator not disclose (orally or in writing) the results of the research until Genentech had been given time to review the disclosure and make recommendations or comment upon it. Thus, 7F3 and 7C2 were not publicly available and the cited reference does not qualify as prior art.

In view of the above, Applicants submit that the presently claimed invention is not anticipated by, or obvious over, Lewis and respectfully request that the Examiner reconsider and withdraw these rejections.

Rejections under §35 U.S.C. §103(a)

On page 4 of the Office Action, Claims 32-36, 39, and 58 have been rejected under 35 U.S.C. §103(a) as being obvious over Shepard et al. or Lewis et al. in view of Fendly et al., Deshane et al., and further in view of Senter et al. Additionally, Claims 42-55 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Shepard et al. in view of Lewis et al. and Fendly et al. and further in view of Deshane et al. and Senter et al.

As set forth above, the presently claimed invention is not taught or suggested by either Shepard or Lewis.

In particular, Shepard teaches the derivation of a family of monoclonal antibodies focused against the extracellular domain of $p185^{HER2}$. (See page 119, left column, lines 16-18). Monoclonal antibodies 4D5, 7C2, and 7F3 are some of these antibodies. (See Table I at page 122). Shepard teaches that these monoclonal antibodies vary in their ability to inhibit proliferation of breast tumor cells, but that 7C2 and 6E9 are consistently less active than the other antibodies in this respect. (See page 120, left column, lines 19-21). Additionally, Shepard discloses that 7C2 has the ability to stimulate the proliferation of several of the tumor

cell lines shown in Table III. (See page 120, right column, lines 4-8). Further, when these antibodies were compared for efficacy, as measured by their abilities to inhibit growth of breast and ovarian tumor cells overexpressing $p185^{HER2}$, muAb 4D5 was generally the most potent and was considered "a good candidate for further characterization." (See page 121, left column, lines 6-9).

Based on these disclosures in Shepard, Applicants submit that one of ordinary skill in the art would not have been motivated to experiment with 7C2 or with antibodies that bind to the same epitope as 7C2 (or 7F3) and surprisingly discover that these antibodies can induce the death of an ErbB2 cell as in the present invention. Without motivation, there cannot be a case of obviousness.

First, as set forth above, Shepard teaches that 7C2 is consistently less active in inhibiting the proliferation of breast tumor cells than the other antibodies shown in Table I. One of skill in the art reading this disclosure in Shepard would be motivated to experiment with an antibody other than 7C2 in experiments in which the inhibition or death of cancerous or tumor cells is desired (e.g., a cell which overexpresses ErbB2 as in the present invention). Thus, this disclosure of Shepard teaches away from the present invention. Second, as discussed above, Shepard discloses that 7C2 actually stimulates the proliferation of certain types of cancers. This is the opposite of the presently claimed invention which induces the death of a cell which overexpresses ErbB2 (e.g., a cancer cell). As a result, one of skill in the art would not be motivated to experiment with 7C2, or antibodies that bind to the epitope that 7C2 binds and arrive at the present invention. Thus, Shepard again teaches away from the presently claimed invention. Finally, the disclosure set forth in Shepard that states that muAb 4D5 is the most potent of the $p185^{HER2}$ antibodies set forth in Table I against breast and

ovarian tumor cells and is the best candidate for further characterization would certainly motivate one of skill in the art to experiment with 4D5, and not 7C2 or 7F3, or antibodies that bind to the epitope to which 7C2 or 7F3 bind.

Although Lewis discloses antibodies 7C2 and 7F3 in passing, Lewis does not teach or suggest the presently claimed invention, i.e., methods for inducing cell death by exposing a cell that overexpresses ErbB2 to an antibody that binds to the epitope to which 7C2 or 7F3 bind. As set forth above, a statement that antibodies that bind to the same epitope inherently have the same properties, without more, is insufficient to draw a conclusion that all antibodies that bind to Domain 1, or even to the epitope on Domain 1 where 7C2 and 7F3 bind, will necessarily have the same characteristics (e.g., induce cell death). Classes of antibodies exist in which antibodies have the same binding domain but behave very differently because they have different constant domains. IgG is but one example. In addition, although antibodies may be able to bind to the same epitope, binding to that epitope may be conformationally dependent. In other words, binding of a particular antibody to a particular epitope may only occur when a particular region is located next to it, or only if that particular region is folded in a particular manner. The folding of the adjacent region could sterically hinder the binding of antigens to the antibody bound to the epitope, and thus may effect certain characteristics of that antibody (e.g., ability to induce death of a cell).

Further, there is no disclosure present in Lewis to motivate one of skill in the art to experiment with 7C2 or with antibodies that bind to the same epitope as 7C2 (or 7F3) and discover that these antibodies induce the death of an ErbB2 cell as claimed in the present application. Without motivation, there cannot be a case of obviousness.

Additionally, the results in Lewis suggest that antibody 4D5 is the most potent of the growth-inhibitory antibody and has the most consistent growth-inhibitory activity towards breast tumor cell lines. (See Lewis, p. 256, left column, lines 45-48 and p. 259, right column, lines 1-3). In particular, Lewis notes that 4D5 had superior growth inhibition of SK-BR-3 (i.e., breast cancer cell). However, a disclosure of growth inhibition of cells does not teach or suggest the inducement of cell death as presently claimed. Thus, one of skill in the art would not arrive at the presently claimed invention based on the disclosure of Lewis. Further, Applicants submit that the disclosures set forth in Lewis would motivate one of skill in the art to experiment with 4D5, and not 7C2 or 7F3, or antibodies that bind to the epitope to which 7C2 or 7F3 bind, and arrive at the present invention (i.e., methods for inducing cell death by exposing a cell that overexpresses ErbB2 to an antibody that binds to the epitope to which 7C2 or 7F3 bind). In fact, these disclosures actually lead one of skill in the art away from the presently claimed invention, i.e., they teach away from the present invention.

In addition, Applicants submit that a disclosure of growth inhibition does not teach or suggest the inducement of cell death as presently claimed. Growth inhibition of cells can occur without cell death occurring. Thus, one of skill in the art would not arrive at the presently claimed invention based on the disclosures of Shepard or Lewis.

It is submitted that the teachings of Fendly, Deshane, and Senter do not make up for the deficiencies of Shepard or Lewis. Thus, Applicants submit that the combination of the Examiner's cited references neither teaches nor suggest the present invention. Further, Applicants submit that the combination of the references would not result in the presently claimed invention. Thus, the present invention is not obvious.

Further, although antibodies 7F3 and 7C2 are mentioned in Shepard, Fendly et al., and Lewis et al., the references do not enable these particular antibodies. In particular, antibodies 7F3 and 7C2 were not deposited with respect to the references and their sequences were not disclosed in the references in such a way that a skilled person could have reproduced those particular antibodies based on the references. The antibodies 7F3 and 7C2 were not publically distributed or publically available more than one year prior to, October 18, 1996, the elective filing date of this application. If an outside investigator had requested samples of the 7F3 or 7C2 antibodies prior to October 17, 1996, Genentech would only have provided the antibodies to the investigator if Genentech was able to approve a research plan proposed by the outside investigator. If the research plan was approved, Genentech would only have provided the research material to the outside investigator under a Material Transfer Agreement (MTA). The standard Genentech MTA at that time imposed restrictions or limitations on the use of the research material. In particular, the laboratory receiving the research material under a Genentech MTA could only use the research material for a research plan approved by Genentech and could not transfer the research material to others outside the laboratory receiving the research material. The MTA further required that the outside investigator not disclose (orally or in writing) the results of the research until Genentech had been given time to review the disclosure and make recommendations or comment upon it. Thus, 7F3 and 7C2 were not publicly available and the cited references do not qualify as prior art.

In view of the above, Applicants submit that the present invention is patentable over Shepard et al. or Lewis et al. in view of Fendly et al., Deshane et al., and further in view of Senter et al. and is also patentable over Shepard et al. in view of Lewis et al. and Fendly et al.

and further in view of Deshane et al. and Senter et al. Accordingly, Applicants respectfully request that these rejections be reconsidered and withdrawn.

CONCLUSION

In light of the above, Applicants believe that this application is now in condition for allowance and therefore request favorable consideration.

If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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4/24/02
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MARKED-UP COPY OF AMENDED CLAIMS

28. (Three Times Amended) A method for inducing cell death comprising exposing a cell which overexpresses ErbB2 to an effective amount of an isolated antibody that binds to an epitope on ErbB2 to which antibody 7C2 or 7F3 bind [that cross-blocks binding of antibody 7C2 or antibody 7F3 to ErbB2].

32. (Twice Amended) The method of Claim 28 further comprising exposing the cell to a second anti-ErbB2 antibody which does not bind to an epitope on ErbB2 to which antibody 7C2 or 7F3 bind [cross-block binding of antibody 7C2 or antibody 7F3 to ErbB2].

34. (Twice Amended) The method of Claim 33 wherein the cell is exposed to the antibody that binds to an epitope on ErbB2 to which antibody 7C2 or 7F3 bind [that cross-blocks binding of antibody 7C2 or antibody 7F3 to ErbB2] before the cell is exposed to the second antibody.

42. (Twice Amended) A method for inducing cell death comprising exposing a cell which overexpresses ErbB2 to an effective amount of a composition comprising an antibody that binds to an epitope on ErbB2 to which antibody 7C2 or 7F3 bind [that cross-blocks binding of antibody 7C2 or antibody 7F3 to ErbB2] and a pharmaceutically acceptable carrier, wherein the antibody results in about 5 to 50 fold induction of annexin binding relative to untreated cell in an annexin binding assay using BT474 cells.

58. (Twice Amended) A method for inducing cell death comprising:

exposing a cell that overexpresses ErbB2 to a first antibody that binds to an epitope on ErbB2 to which antibody 7C2 or 7F3 bind [cross-blocks binding of antibody 7C2 or antibody 7F3 to ErbB2]; and

subsequently exposing the cell to a second antibody that binds to a domain of ErbB2 other than the binding site of antibody 7C2 or antibody 7F3.